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# Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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	Application No.	Applicant(s)	
	10/568,669	AGUS ET AL.	
Office Action Summary	Examiner	Art Unit	
	Stephen L. Rawlings	1643	
The MAILING DATE of this communication app Period for Reply	ears on the cover sheet with the c	orrespondence addres.	s
A SHORTENED STATUTORY PERIOD FOR REPLY WHICHEVER IS LONGER, FROM THE MAILING DA  - Extensions of time may be available under the provisions of 37 CFR 1.13 after SIX (6) MONTHS from the mailing date of this communication.  - If NO period for reply is specified above, the maximum statutory period w  - Failure to reply within the set or extended period for reply will, by statute, Any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).	ATE OF THIS COMMUNICATION 36(a). In no event, however, may a reply be time will apply and will expire SIX (6) MONTHS from cause the application to become ABANDONE	I. ely filed the mailing date of this commur (35 U.S.C. § 133).	
Status			
<ul> <li>1) ☐ Responsive to communication(s) filed on 25 No.</li> <li>2a) ☐ This action is FINAL.</li> <li>2b) ☐ This</li> <li>3) ☐ Since this application is in condition for allowant closed in accordance with the practice under E</li> </ul>	action is non-final. nce except for formal matters, pro		rits is
Disposition of Claims			
4) ☐ Claim(s) 31-37 is/are pending in the application 4a) Of the above claim(s) is/are withdraw 5) ☐ Claim(s) is/are allowed. 6) ☐ Claim(s) 31-37 is/are rejected. 7) ☐ Claim(s) is/are objected to. 8) ☐ Claim(s) are subject to restriction and/or	vn from consideration.		
Application Papers			
9) ☐ The specification is objected to by the Examiner 10) ☐ The drawing(s) filed on 16 February 2006 is/are Applicant may not request that any objection to the c Replacement drawing sheet(s) including the correction 11) ☐ The oath or declaration is objected to by the Examiner	e: a) accepted or b) objected drawing(s) be held in abeyance. See on is required if the drawing(s) is obj	937 CFR 1.85(a). ected to. See 37 CFR 1.	, ,
Priority under 35 U.S.C. § 119			
12) Acknowledgment is made of a claim for foreign  a) All b) Some * c) None of:  1. Certified copies of the priority documents  2. Certified copies of the priority documents  3. Copies of the certified copies of the prior  application from the International Bureau  * See the attached detailed Office action for a list of	s have been received. s have been received in Applicati ity documents have been receive I (PCT Rule 17.2(a)).	on No ed in this National Stag	e
Attachment(s)  1) Motice of References Cited (PTO-892)	4) 🔲 Interview Summary		
Notice of Draftsperson's Patent Drawing Review (PTO-948)     Information Disclosure Statement(s) (PTO/SB/08)     Paper No(s)/Mail Date	Paper No(s)/Mail Da 5) Notice of Informal P 6) Other:	te	

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#### **DETAILED ACTION**

### Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 25, 2009, has been entered.

- 1. The amendment filed November 3, 2009, has been entered. Claims 10-19, 29, and 30 have been canceled. Claims 35-37 have been added.
- 2. Claims 31-37 are pending in the application and are currently under prosecution.

#### Response to Amendment

3. The declaration under 37 C.F.R. § 1.132 by Anjali Jain, which was filed on November 3, 2009, is sufficient to overcome the rejection of the claims under 35 U.S.C. § 102(a) as being anticipated by Hedvat et al.

# Grounds of Objection and Rejection Withdrawn

4. Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed September 8, 2009.

#### Response to Arguments

5. Applicant's arguments with respect to claims 31-33 have been considered but are moot in view of the new ground(s) of rejection.

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### New Grounds of Objection

# Specification

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claims 31 and 34-37 are drawn to a method of treating prostate cancer in a mammal comprising administering R-etodolac on "an R-etodolac periodic basis" and administering a recombinant humanized monoclonal antibody 2C4 on "a 2C4 periodic basis".

M.P.E.P. § 608.01(o) states:

While an applicant is not limited to the nomenclature used in the application as filed, he or she should make appropriate amendment of the specification whenever this nomenclature is departed from by amendment of the claims so as to have clear support or antecedent basis in the specification for the new terms appearing in the claims. This is necessary in order to insure certainty in construing the claims in the light of the specification, *Ex parte Kotler*, 1901 C.D. 62, 95 O.G. 2684 (Comm'r Pat. 1901). See 37 CFR 1.75, MPEP § 608.01(i) and § 1302.01.

M.P.E.P. § 608.01(o) further states that if the examiner determines that the claims presented in prosecution do not comply with 37 CFR 1.75(d)(1), applicant will be required to make appropriate amendment to the description to provide clear support or antecedent basis for the terms appearing in the claims, provided no new matter is introduced.

It is submitted that it would not be clear from a reading of the descriptive portion of this application, alone, where there is support for the language of the claims because although the specification describes "a NSAID periodic basis" and "a Her-kinase axis inhibitor periodic basis", it does not describe the claimed "an R-etodolac periodic basis" or the claimed "a 2C4 periodic basis". Moreover, the "NSAID" to which the term "a NSAID periodic basis" refers is not necessarily R-etodolac, such that the claimed "R-etodolac periodic basis is not necessarily equivalent to the disclosed "NSAID periodic basis"; and similarly, the "Her-kinase axis inhibitor" to which the term "a Her-kinase axis

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inhibitor periodic basis" refers is not necessarily monoclonal antibody 2C4 or a humanized version thereof, such that the claimed "2C4 periodic basis" is not necessarily equivalent to the disclosed "Her-kinase axis inhibitor periodic basis".

## Claim Objections

7. Claims 31 and 34-37 are objected to under 37 CFR 1.75(c), as failing to conform to the invention as set forth in the remainder of the specification, where the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description. See M.P.E.P. § 608.01(g).

There is no written support in the descriptive portion of this application, as originally filed, for the claim terms "an R-etodolac periodic basis" and "a 2C4 periodic basis".

Appropriate correction is required (i.e., Applicant should make appropriate amendment to the description to provide clear support or antecedent basis for the terms appearing in the claims, as in accordance with the guidance set forth under M.P.E.P. § 608.01(o)).

Applicant is however cautioned against the introduction of new matter; and in light of the fact that claim 31 is not an original claim, it is suggested that Applicant amend claim 31 to recite, for example, "administering to said mammal daily a quantity of R-etodolac and administering to said mammal twice weekly a quantity of a recombinant humanized version of monoclonal antibody 2C4".

# New Grounds of Rejection

### Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

<sup>&</sup>lt;sup>1</sup> In particular, see paragraph [0035] of the published application (i.e., U.S. Patent Application Publication No. 2007/0104714-A1.

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designations to define completely distinct antibodies.

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9.

Claims 31-37 are rejected under 35 U.S.C. 112, second paragraph, as being

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indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention.

Claims 31-37 are indefinite for the following reasons:

The claims are indefinite in the use of the designation "2C4" as the sole (a) means of identifying claimed plurality of recombinant humanized monoclonal antibodies. The use of laboratory designations only to identify a particular antibody renders the claims indefinite because different laboratories may use the same laboratory

In addition, it is submitted that the recitation of the term "a recombinant humanized monoclonal antibody 2C4" renders the claims indefinite because not only is it not evident to which antibodies the claims refer but also it cannot be ascertained what structural and functional properties members of the claimed plurality of antibodies must have<sup>2</sup>. For example, it is not evident to which antigen the claimed antibody must bind; it is also not evident how the antibody is "humanized" or derived from another antibody; and it is not apparent from what other antibody the claimed antibody is necessarily derived. Moreover, it is not apparent if the claimed humanized antibody must comprise heavy and light chain variable regions comprising each of the six complementarity determining regions (CDRs) of the antibody from which it is derived or whether it must have or retain the antigen binding specificity of the antibody from which it is derived.

<sup>&</sup>lt;sup>2</sup> Although the specification describes, for examples, publications that describe antibodies having this particular designation, i.e., "2C4", the claims are not necessarily limited to those antibodies; and besides, Applicant is duly reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, since the publication describing an antibody designated "2C4", which is referred to by the disclosure in paragraph [0007], for example, of the published application, is non-patent literature, Applicant is further reminded that M.P.E.P. § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications (e.g., Agus et al.). Notably "essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)".

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It is suggested that this issue might be remedied by amending the claims to include the depository accession numbers of hybridomas or other cell lines producing the claimed monoclonal antibodies. This is because deposit accession numbers are unique identifiers which unambiguously define a given hybridoma or other type of cell line and/or the monoclonal antibody that is produced by a given hybridoma or cell line.

(b) Claims 31 and 34-37 are indefinite because claim 31 recites the terms "an R-etodolac periodic basis" and "a 2C4 periodic basis", where because these terms are not used in the disclosure (and are not defined therein), it cannot be ascertained what is meant by the terms. Given this fact the claims cannot be unambiguously construed and as such the claims fail to delineate the metes and bounds of the subject matter that is regarded as the invention with the necessary clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

It is suggested that this issue be remedied by amending claim 31 to recite, for example, "administering to said mammal daily a quantity of R-etodolac and administering to said mammal twice weekly a quantity of a recombinant humanized version of monoclonal antibody 2C4".

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 31-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. M.P.E.P. § 2164.01 states:

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242

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U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

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There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claims 31-37 are directed to "a recombinant humanized monoclonal antibody 2C4".

The specification does not teach one to make these antibodies by, for example, disclosing their amino acid sequences or the polynucleotide sequences encoding their amino acid sequences. Furthermore, it is unclear if a cell line (e.g., a hybridoma) that produces an antibody having the exact structural and chemical identity as that to which the claims are directed is known and publicly available, or can be reproducibly isolated without undue experimentation. Without access to a hybridoma or recombinant cell line producing the monoclonal antibodies to which the claims are directed, it would not be

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possible to practice the claimed invention, because it would not be possible to make the antibody.

The exact replication of the antibody or a cell producing the same antibody, the exact determination of its amino acid sequence and/or the exact determination of a polynucleotide sequence encoding it are unpredictable events.

It is noted that the specification discloses that Applicant acquired "2C4" from 2C4 Genentech in San Francisco, California; but it is not known whether anyone else might acquire this antibody from Genentech or under what conditions.

Applicant is duly reminded therefore that M.P.E.P. § 2404.01 states to avoid the need for a deposit, biological materials must be known <u>and</u> readily available - *neither* concept alone suffices.

Therefore it is suggested that a suitable biological deposit of a hybridoma or other cell line producing the claimed antibody is needed in this case to satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph; see 37 C.F.R. §§ 1.801-1.809.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicant or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth under 37 CFR §§ 1.801-1.809 have been met.

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If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Furthermore, if it does not already do so, the specification should be amended to provide requisite information regarding such deposits (i.e., specific reference to the deposited material by the name of the depository and its accession number, which further provides the depository's address and the date the deposit was made). See 37 CFR § 1.809 (d).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

### Claim Rejections - 35 USC § 103

- 12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
  - (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
- 13. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
  - 1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.

- 3. Resolving the level of ordinary skill in the pertinent art.
- 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agus et al. (*Cancer Cell.* 2002 Aug; **2** (2): 127-137) and Kamijo et al. (*Int. J. Urol.* 2001; **8**: S35-S39).

Claims 31-37 are drawn to a method comprising administering to a mammal an amount of R-etodolac and an amount of a humanized version of monoclonal antibody 2C4, wherein R-etodolac is administered daily as a dose of about 100 to about 500 mg/kg and wherein the antibody is administered twice weekly as a dose of about 5 to about 40 mg/kg.

Agus et al. teaches the inhibition of tumors in mice inoculated with prostate cancer cells by administering to the mice an amount of a murine monoclonal antibody designated 2C4 and a humanized version thereof; see entire document (e.g., the abstract; page 131, column 2). Agus et al. teaches the antibodies were administered by intraperitoneal injection to the mice in an initial dose of 6, 20, or 60 mg/kg, followed by twice weekly injections of 3, 10, or 30 mg/kg; see, e.g., page 132, Figure 5.

Kamijo et al. teaches the induction of apoptosis of prostate cancer cell lines upon treatment of the cells with etodolac; see entire document (e.g., page S36, column 2). Kamijo et al. teaches the cells were cultured in the presence of etodolac at a concentration of up to 10<sup>-5</sup> M (see, e.g., page S36, column 2). Although etodolac induced apoptosis of prostate cancer cells in a dose-dependent manner, it had no such effect on normal prostate cells; see, e.g., page S37, column 1.

Although Kamijo et al. does not expressly teach that etodolac contains the R-enantiomer, etodolac is a commercially available NSAID containing a racemic mixture of both S- and R-enantiomers; accordingly, absent a showing otherwise, it is submitted to be evident that the etodolac used by Kamijo et al. to induce apoptosis of prostate

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cancer cells in culture contained an amount of R-etodolac, which was sufficient to induce the cells to undergo apoptosis.

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to combine the modes of treatment described by Agus et al. and Kamijo et al. to administer to a mammal, such as a mouse or a human, an amount of the monoclonal antibody designated 2C4 or a humanized version thereof, and an amount of etodolac (commercially available as a racemic mixture of both S- and R-enantiomers) to treat prostate cancer in the mammal. This is because Agus et al. teaches the inhibition of tumors in mice inoculated with prostate cancer cells by administering to the mice an amount of the monoclonal antibody designated 2C4 or a humanized version thereof and because Kamijo et al. teaches the induction of apoptosis of prostate cancer cell lines upon treatment of the cells with etodolac.

Then, with regard to claims 33 and 34, although Kamijo et al. does not expressly teach that etodolac is administered daily to a mammal to treat prostate cancer or that it is administered to the mammal in a dose of about 100 to about 500 mg/kg, it is nevertheless a common objective in the art to establish a dose that is both safe and effective<sup>3</sup>, so as achieve optimal therapeutic effect and maximal benefit. See In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." (citations omitted)). See In re Peterson, 65 USPQ2d 1379 1382 (CA FC 2003): "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to establish a dose that is both safe and effective, so as achieve optimal therapeutic effect and maximal benefit; and here there is a presumption that such a dose would fall within the claimed range of about 100 to about 500 mg/kg.

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<sup>&</sup>lt;sup>3</sup> This is often initially achieved in pre-clinical experiments using mice, such as those described by Agus et al., in which the dose of the drug is varied and the results (endpoints) are then correlated with the doses administered.

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### Conclusion

#### 15. No claim is allowed.

16. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Glaser et al. (Eur. J. Pharmacol. 1995 Jul 25; 281 (1): 107-111) teaches the selective inhibition of human PGHS-2 by etodolac. Santini et al. (Apoptosis. 1999 Jun; 4 (3): 151-62) teaches weak PGHS-2 inhibitors promote apoptosis to provide better understanding of the cyclooxygenase-dependent and cyclooxygenase-independent mechanisms by which PGHS-2 inhibitors cause antiproliferative effects. Song et al. (J. Natl. Cancer Inst. 2002 Apr 17; 94 (8): 585-591) teaches dissociation of the cyclooxygenase-2 (COX-2)-inhibiting and apoptosis-inducing activities of COX-2 inhibitors upon prostate cancer cells. Chen et al. (Cancer Sci. 2003) Mar; 94 (3): 253-258) teaches the induction of apoptosis of colon cancer cells by treatment with etodolac. Mendoza et al. (Cancer Res. 2002 Oct; 62: 5485-5488) teaches an anti-HER2 recombinant humanized antibody designated 2C4 is capable of inhibiting tumor growth in mice inoculated with prostate cancer cells. Albanell et al. (Adv. Exp. Med. Biol. 2003; 532: 253-268) teaches the mechanisms of action of anti-HER2 antibody 2C4.

Also made of record, Lu et al. (*Proc. Natl. Acad. Sci. U S A.* 2004 Mar 2; **101** (9): 3118-3123) teaches R-etodolac induces B-CLL cells to undergo apoptosis. Jensen et al. (*Invest. New Drugs.* 2008; **26**: 139-149) teaches the results of a phase I study of R-etodolac in patients with B-CLL. Yasui et al. (Blood. 2005 Jul 15; **106** (2): 706-712) teaches SDX-101, the R-enantiomer of etodolac, induces cytotoxicity, overcomes drug resistance, and enhances the activity of dexamethasone in multiple myeloma. Kolluri et al. (*Proc. Natl. Acad. Sci. U S A.* 2005 Feb 15; **102** (7): 2525-2530) teaches the R-enantiomer of the nonsteroidal antiinflammatory drug etodolac binds retinoid X receptor and induces prostate tumor-selective apoptosis.

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18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/ Primary Examiner, Art Unit 1643

slr March 10, 2011